PROJECT

Tutor's Name	Monica Montopoli
Cotutor's Name	Andrea Alimonti

1) Project title
Discovering Natural Senolytic Agents for Age-Related Disease
2)Abstract (max 500 words)

The increasing age of populations in high-income countries correlates with a rise in age-related disorders, including cardiovascular diseases, cancer, metabolic diseases, and neurodegenerative conditions. These diseases significantly impact the quality of life for the elderly and pose substantial societal and economic challenges. Contemporary aging research aims to extend health-span—the period of good health—rather than merely increasing lifespan.

Addressing aging holistically, instead of targeting individual pathologies, may offer a more effective approach to combating age-related disorders and enhancing elderly health. This perspective has sparked growing interest in identifying safe and potent anti-aging drugs.

Aging is a multifaceted process influenced by both genetic and environmental factors. One key biological driver of aging is the accumulation of senescent cells. These cells, while unable to proliferate, continue to secrete various molecules collectively known as the Senescence-Associated Secretory Phenotype (SASP). As organisms age, senescent cells amass in tissues, and through SASP, can induce tissue damage, actively contributing to the aging process. Research has shown that selectively removing senescent cells can extend lifespan and improve health in aged animal models. Consequently, developing senolytic molecules—compounds that selectively eliminate senescent cells—represents a promising anti-aging strategy. However, current senolytics often exhibit general toxicity.

This project's primary objective is to identify natural sources of safe and effective anti-aging compounds that target cellular senescence. The project will unfold in three phases:

1. Development of a high-throughput screening platform for senolytic compound identification:
   - Research and acquire screening libraries, with a focus on natural products.
   - Generate an appropriate cellular model for identifying senescence-targeting molecules.
   - Conduct high-throughput screening in partnership with the University of Padova's Biology Department facility.
2. *In vitro* validation and selection of promising hits:
   - Validate identified hits across a panel of cell lines.
   - Identify molecules suitable for pharmaceutical development.
3. Experimentation on *in vivo* aging models:

- Test selected molecules on mouse models, including the p16-luciferase transgenic mouse (which expresses a senescence reporter gene) and naturally aged mice. - Evaluate the efficacy of tested molecules and determine which age-related pathologies are most likely to benefit from the therapeutic intervention.